EMBL Group Leader Lecture
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The Moesgaard Museum Auditorium

Structural basis and mechanism of the selective autophagy receptor p62/SQSTM1

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The multifunctional signaling adaptor and selective autophagy receptor p62/SQSTM1 is commonly found in dense light-microscopic loci of eukaryotic cells. Recently, Ciuffa et al. demonstrated that p62 is able to form organized polymers of helical symmetry once purified and reconstituted in the test tube [1]. In selective autophagy, p62 acts both as a substrate and as a receptor to bridge LC3 attached to the autophagosomal membrane with ubiquitinated cargo destined for degradation in the lysosome [2]. In signaling, p62 acts as an adaptor protein by interacting with protein kinases (atypical protein kinase C, MEKK3, MEK5, ERK1 and RIP) and ubiquitin ligases such as TRAF6 and the KEAP1-Cul3 complex [3]. In the talk, I will present a cryo-EM structural analysis of p62. Together with structures of assemblies from the PB1 domain we show that p62 is organized in flexible polymers with the PB1 domain constituting a helical scaffold. We determined the ~10 Å resolution structures of a series of PB1 constructs and found that isolated PB1 domains have the ability to form flexible helical filaments (Figure 1). Using biochemical assays, we demonstrated that the p62 filamentous assemblies interact with their biologically relevant binding partners LC3 and ubiquitin. These studies provide first structural insights into how p62 assemblies recognize ubiquitylated cargo while at the same time they can act as a scaffold for the nascent autophagosome.

References

1) Ciuffa, R. et al. Cell Rep. 2015; 11:748-758. 2) Johansen, T. et al. Autophagy. 2011; 7:279-296. 3) Moscat, J. et al. Trends. Biochem. Sci. 2012; 37:230-236.

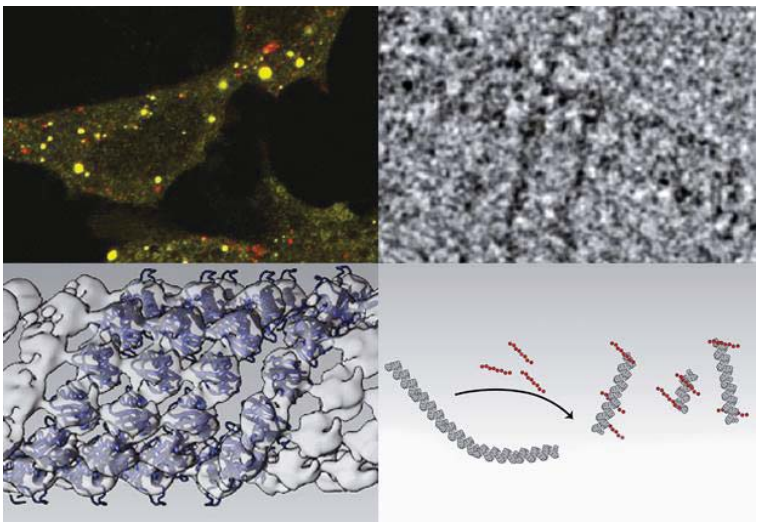

Figure 1
Structure and mechanism of assembly of p62/SQSTM1 into helical filaments. p62 localizes to dense punctae in cells as observed by light microscopy (upper left). Once purified, p62 assembles into a helical scaffold formed from the PB1 domain (micrograph upper right, 3D reconstruction lower left). We found that addition of poly-ubiquitin chains induces disassembly of filaments (lower right).